I. REMARKS

Claims 25-27 and 43-66 are presently pending in this application. Claims 46-54 have been withdrawn pursuant to a restriction requirement. Claims 25-27, 43-45 and 55-66 stand variously rejected under 35 U.S.C. §§ 102 and 103. Reconsideration of the application is requested in view of the following remarks.

Rejections Under 35 U.S.C. § 102

Claims 25-27, 43-45 and 55-57 are rejected under 102(b) as allegedly anticipated by Heldin et al. (Nature 319:511-514, 1986, hereinafter "Heldin"). In support of this allegation, the Office states that Heldin discloses a protein preparation that is "free of other human proteins." (Office Action, page 4). The Office further asserts that Applicants' evidence (*e.g.*, Cousens and Betsholtz Declarations) that the methods of Heldin will result in a protein preparation that is contaminated with other human proteins is insufficient to demonstrate the actual presence of an impurity. (Office Action, page 5). In sum, the Office continues to maintain that Heldin discloses all the limitations of the pending claims.

Applicants traverse the rejection and supporting remarks.

It is well-settled claims are anticipated only if a single reference expressly or inherently discloses all the limitations of the claims. *See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc.,* 231 USPQ 81, 90 (Fed. Cir. 1986). Moreover, the single reference must disclose all of the claimed elements "arranged as in the claim." *See, e.g., Richardson v. Suzuki Motor Co.* 9 USPQ2d 1913, 1920 (Fed. Cir. 1989). To support an anticipation rejection based on inherency, the Office must provide factual and technical grounds establishing that the inherent feature necessarily flows from the teachings of the reference. *See, e.g., Ex parte Levy*, 17 USPQ2d 1461, 1464 (BPAI 1990). Inherency cannot be established by probabilities or possibilities. *See, e.g., Continental Ca Co. USA, Inc. v. Monsanto Co.* 20 USPQ2d 1746, 1749 (Fed. Cir. 1987).

Furthermore, with regard to purified biological products, the CCPA has stated that anticipation is avoided if a claimed composition is of increased purity:

> "by definition, pure materials necessarily differ from *less* pure or impure materials and, if the latter are the only ones existing and available as a standard of reference ... perforce the "pure" materials are "new" with respect to them ... [W]hether the claimed pure materials have the same usefulness or assortment of properties as the impure materials of the prior art." *In re Bergstrom*, 166 USPQ 256, 262 (CCPA 1970).

Applying these rules to the pending case, Applicants submit that the claimed compositions are distinguishable, and superior to, the preparations of the prior art. Applicants' claims are directed to recombinant protein preparations produced in a nonhuman cell such that the protein preparation is free of other human proteins. Prior to the present invention, significant amounts of human PDGF could not be readily isolated and, in addition, these isolated protein preparations were necessarily contaminated with other human proteins. Thus, the claimed invention solves both the problem of contamination and the problem of obtaining commercial amounts of human protein.

Heldin fails to expressly or inherently disclose a protein preparation produced recombinantly from nonhuman cells. Rather, Heldin discloses that PDGF protein can be isolated from a human osteosarcoma cell line. Furthermore, there can be no inherent disclosure of a recombinantly produced protein because Heldin contains no teachings regarding the nucleotide sequence encoding the protein; no teachings regarding cloning methods; and no teachings regarding techniques for purifying recombinantly produced proteins. Thus, Heldin does not disclose a recombinant protein preparation made from nonhuman cells.

In addition to failing to teach a recombinantly produced protein, Heldin's protein preparation is not free of other human proteins. Indeed, as set forth in the Cousens Declaration (and supported a by reference authored by a Nobel laureate), the statement that "methods of purifying proteins from human sources ... cannot result in a protein

product free of contaminating human proteins is indeed accurate." (Cousens Declaration, paragraph 3; see also, Betsholtz Declaration filed March 2, 1998, paragraphs 5 and 6, stating "the methods described in Heldin would not produce ODGF preparations completely free of other human proteins" and that "it would not be possible to produce preparations having [such] purity without the gene encoding PDGF. Heldin does not describe the gene or recombinant methods for producing PDGF A-chain."). Thus, in stark contrast to Heldin's protein preparation, the claimed, recombinantly produced protein preparation would be "free of human protein contaminants and devoid of contaminating human viruses." (Cousens Declaration, paragraph 7 and Betsholtz Declaration, paragraph 6). In sum, Heldin does not disclose key elements of the pending claims and, accordingly, does not anticipate the claimed invention.

Applicants also traverse the Examiner's assertion that the presence of yeast (or other eukaryotic) ubiquitin necessarily means that human protein is present. (Office Action, page 4). Even if the amino acid sequence of a yeast protein is the same as the human, the protein is still a "yeast" protein because it is made by translation of yeast codons using yeast amino acids. In addition, the protein will contain post-translational modifications characteristic of yeast, not human, cells. Thus, even yeast proteins with the same amino acid sequence are not "human" proteins.

In sum, Applicants submit that Heldin fails to expressly or inherently disclose all of the elements of the pending claims. Accordingly, claims 25-27, 43-45 and 55-57 are not anticipated by this reference and withdrawal of this rejection is respectfully requested.

Rejections Under 35 U.S.C.§ 103(a)

Claims 55-57 stand rejected as allegedly obvious over Heldin. It is maintained that it would have been obvious to a skilled artisan to arrive at the claimed invention in view of Heldin's disclosure.

Applicants traverse.

In order to render claims obvious, the burden is on the Office to establish that the reference teaches all the limitations of the claimed invention and, moreover, suggests the desirability of arriving at the claimed subject matter. (*See, e.g., Amgen, Inc. v. Chugai Pharm. Co.,* 18 USPQ2d 1016, 1023 (Fed. Cir. 1991) stating that "hindsight is not a justifiable basis on which to find that the ultimate achievement of along sought and difficult scientific goal was obvious" and *In re Laskowski,* 10 USPQ2d 1397, 1399 (Fed. Cir. 1989) stating that "the mere fact that the prior art could be so modified would not have made the modification obvious unless the prior art suggested the desirability of the modification.") For the reasons outlined above, Heldin does not teach all the limitations of the pending claims. There is no teaching or suggestion to recombinantly produce a protein preparation that is free of other human proteins. Furthermore, Heldin is silent as to the "desirability" of the claimed methods. There is no suggestion in this reference that it would be desirable to (1) use recombinant methods to produce a PDGF A-chain homodimer or (2) obtain a protein preparation of PDGF A-chain homodimers that is free of other human proteins. Accordingly, the Office has not met its burden and a *prima facie* case of obviousness has not been established.

Applicants also note that the Board of Patent Appeal and Interferences has determined that recombinantly produced proteins are not necessarily obvious over the same proteins produced from natural sources. *See, e.g., Ex parte Goeddel,* 5 USPQ2d 1449 (BPAI, 1987). In *Ex parte Goeddel*, the Examiner rejected claims to recombinantly produced human leukocyte interferon as allegedly obvious over references disclosing purification of these proteins from natural sources. The Board overturned the rejection, finding the claims non-obviousness and stating:

> "the statutory inquiry is obviousness and not 'differ in kind'. What that means, palpably it is not a proper basis for a rejection. ...
> [Applicants] have pointed out in great detail how the claimed synthetic mature human leukocyte interferons prepared by recombinant DNA technology differ from the natural human leukocyte interferons purified from natural sources of the prior art." *Ex parte Goeddel,* at 1450-1451.

In the pending case, Applicants have properly addressed the statutory inquiry of obviousness and, for the reasons detailed above, submit that the Office has failed to meet their burden of establishing *prima facie* obviousness. In addition, Applicants have pointed out how the recombinantly produced protein of the claimed invention differs from that isolated from human cells, for example, for all the reasons set forth in the Cousens Declaration and accompanying Amendment filed on June 17, 1999. In view of the evidence of record, Applicants submit that the pending claims, directed to a recombinantly produced human protein that is free of other human proteins, is not obvious in view of the reference that discloses a human protein isolated from human cells. Accordingly, the rejection is improper and Applicants request that it be withdrawn.

II. CONCLUSION

In view of the foregoing, Applicants submit that the claims are now in condition for allowance and request early notification to that effect.

Please direct all further communications regarding this application to:

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